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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	**PAPER NUMBER**
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/19/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/626,229	REUBI, JEAN-CLAUDE	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-9,12-14,23-25,28,29 and 31-36* is/are pending in the application.

4a) Of the above claim(s) *1-3,6-9,23-25 and 32-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-14, 28-29 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner of the application has changed. This case has now been transferred as of 7/10/2006. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Brandon Fetterolf, Group Art Unit 1642.

Response to the Amendment

The Amendment filed on 09/06/2006 in response to the previous Non-Final Office Action (04/11/2006) is acknowledged and has been entered.

Claims 1-3, 6-9, 12-14, 23-25, 28-29 and 31-36 are currently pending.

Claims 1-3, 6-9, 23-25 and 32-36 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 12-14, 28-29 and 31 are currently pending.

Information Disclosure Statement

The Information Disclosure Statement filed on 09/06/2006 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained but Modified in view of Amendments and Arguments:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12 and 28-29 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising, in addition to a pharmaceutically acceptable carrier material and, if desired, at least one pharmaceutically acceptable adjuvant, as the active substance, a derivatized peptide having the formula H--$(Xaa)_n$-$(Xbb)_m$-Try-Xcc-Gly-Trp-Xdd-Asp-Phe-R2, wherein Xaa is Asp, m is 0, Xcc is Met, Leu or Nle and Xdd is Met, or Nle, wherein a chelating group is bound to an amide bond or through a spacing group to the N-terminal amino acid residue of said peptide, does not reasonably provide enablement for a pharmaceutical composition comprising, in addition to a pharmaceutically acceptable carrier material and, if desired, at least one pharmaceutically acceptable adjuvant, as the active substance, a peptide of the general formula H--$(Xaa)_n$-$(Xbb)_m$ -Try-Xcc-Gly-Trp-Xdd-Asp-Phe-R2 (SEQ ID NO: 27), wherein a chelating group is bound by an amide bond or through a spacing group to the N-terminal amino acid residue of said peptide; (Xaa)n stands for 0 to 25 amino acid moieties which are equal or different and are selected from Ala, Leu, Asn, Dpr, Gln, Glu, Ser, Ile, Met, His, Asp, Lys, Gly, Thr, Pro, Pyr, Agr, Trp, Val and Phe; m=0 or 1; Xbb is Asp, Dpr, Glu, or pyr; with the provisio that Xbb can only be Pyr when X=0; Xcc is Met, Leu or Nle; Xdd is Met, Leu or Nle; and R_2 is a hydroxyl group, an acetoxy group or an amino group for the reasons set forth in the prior office action and for the reasons set forth below.

(Note: In the previous Office Action, three rejections under 35 USC 112, 1st paragraph were made. In essence, the rejections set forth that only a composition comprising SEQ ID NO: 21 were enabled for in vitro methods. It is noted that Applicants have amended the claims to remove the recited use, as well as provided arguments thereto. In view of these amendments and arguments set forth below, the Examiner has modified the three previous enablement rejection into one.)

In response to the previous rejection, Applicants provide the following arguments: First, Applicants assert that the currently pending claims are drawn to a composition and are not limited by a recited use. As MPEP 2164.01(c) states: "[In contrast,] when a compound or composition is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of the claim is sufficient to preclude a rejection for nonenablement based on how to use." As such, Applicants assert that the previous Examiner's arguments alleging lack of in vivo efficacy of the claimed invention as a diagnostic or therapeutic agent are thus irrelevant to the currently pending

composition claims. Secondly, Applicants assert that case law has repeatedly held that Applicants need not demonstrate in vivo or other efficacy to meet either the utility requirements of 35 USC 101 or the enablement requirements of 35 USC 112. For example, Applicants submit that the courts have consistently held that the Applicants simply need only demonstrate a reasonably correlation between the activity in question and the asserted utility. In this regard, Applicants assert that this has been clearly demonstrated in Examples 4-7 of the specification by the specific binding of the derivatized labeled peptides to CCK-B receptors in tumor tissue which is recognized by those skilled in the art as being an important indicator of potential in vivo activity. In this case, Applicants assert that the labeled peptides and methods disclosed and fully enabled have been used to image CCK-B receptors expressing tumors in human patients (Kwekkeboom et al. Eur. J. Nucl. Med. 2000; 27: 1312, IDS 3/24/2004). Thirdly, Applicants assert that the specification provides in vitro working examples of derivatized peptides binding to CCK-receptors. For example, Applicants submit that Figure 2 shows the ability of compounds 19-24 to retain affinity of the CCK-B-receptor after substitution have been made to SEQ IDNO: 27 at positions Xbb (i.e., Asp, D-Asp and Dpr), Xcc(i.e., Met, Nle, and thr) and Xdd (i.e., Met and Nle). CCK-receptors, wherein amino acids substitutions at positions Xbb, Xcc and Xdd and the addition of the chelator.

In response to Applicants assertions that the amended claims are drawn to a composition and not limited by a recited use, the Examiner concedes that Applicants have amended the claims to remove the recited intended use, i.e., external imaging or combating/controlling tumors. However, the Examiner recognizes that the amended claims are still drawn to a pharmaceutical composition, wherein the recitation of "pharmaceutical" inherently suggests an in vivo use. Thus, when a compound or composition claim is limited by a particular use, i.e., in vivo use, enablement of that claim should be evaluated based on that limitation. See In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (claiming a chimeric gene capable of being expressed in any cyanobacterium and thus defining the claimed gene by its use). As such, the previous Examiner's arguments pertaining to the lack of in vivo efficacy of the claimed invention, in particular the lack of correlation between in vitro results and in vivo results are relevant to the claimed pharmaceutical composition for its in vivo use as a diagnostic or therapeutic agent. Along the same lines of in vivo efficacy, the Examiner acknowledges that Applicant's need not demonstrate in vivo efficacy to meet the utility requirements of 35 USC 101 and that one needs to only show a reasonably correlation

between the activity and the asserted utility. However, the Examiner recognizes that the instant rejection is not a utility rejection under 35 USC 101, wherein binding of various peptide derivatives to CCK receptors clearly establishes the asserted utility, but is based on eight different factors which need to be considered in determining whether undue experimentation is required. These factors include (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art. In the instant case, while the specification provides specific binding of the derivatized labeled peptides to CCK-B receptors in tumor tissue, the specification appears to be silent on a correlation between the in vitro results, i.e., binding to tumor tissue, and in vivo success. As noted in the prior office action on page 10, those of skill in the art recognize that in vitro assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlation in vitro results to in vivo success, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written. Regarding Applicants submission of Kwekkeboom et al., the Examiner appreciates Applicants pointing out the clinical efficacy of a single species of SEQ ID NO: 27, i.e., Kwekkeboom et al. Eur. J. Nucl. Med. 2000; 27: 1312, IDS 3/24/2004. However, the Examiner recognizes that the reference does not appear to be commensurate in scope with the genus of derivatized peptides encompassed by the amino acid sequence of SEQ ID NO: 27 because the reference provides an octapeptide with activity, but the claims encompass peptides up to 31 amino acids in length.

New objections/Rejections Upon Reconsideration:

Claim Objections

Claim 31 is objected to because the claim contains the character "(I)" in the general formula, but does not appear to define what (I) represents. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 12, 28-29 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Margerium et al. (WO 95/24225 A1, 1995) in view of Fang et al. (US 5,631,230).

Margerium et al. teach polychelant compounds which are useful in diagnostic imaging procedures and which are degradable in vivo to release excretable fragments (Abstract). Specifically, the WO document teaches a polychelant conjugate, wherein the polychelant conjugate is conjugated though a backbone molecule to a biodistribution modifier such as a site directed molecule which can be used to enhance images and/or to deliver cytotoxic doses or radioactivity to targeted cells, tissues, organs and/or body ducts (page 9, 1st paragraph and page 31, 1st paragraph). With regards to the polychelants, the WO document teaches that the polychelants comprise macrocyclic chelates such as DOTA (page 22, 2nd full paragraph). With regards to the site-directed molecules, the WO document teaches that the site-directed molecules include any molecule that naturally concentrates in a selected target organ, tissue, cell or group of cells, in vivo including, but not limited to CCK (page 29, last paragraph). The WO document further teaches that metal ions such as 111 In can be incorporated into the polychelate, wherein the choice of the metal ion depends on the desired therapeutic or diagnostic outcome (page 24 last paragraph to page 25). Moreover, the WO document teaches a pharmaceutical composition comprising said conjugate formulated with conventional pharmaceutical aids such as emulsifiers (page 40, 1st full paragraph). In addition to the

conjugate, the WO document teaches a method of preparing a polychelant conjugate comprising first incorporating a metal into the bifunctional chelate prior to the attachment of the site-directed molecule and attaching the polychelator to targeting moiety through a backbone polymer using well-known heterobifunctional coupling agents (page 33, 2nd full paragraph). Thus, while Margerium et al. do not explicitly teach that attachment through the N-terminal amino acid

Margerium et al. do not explicitly teach that the CCK peptide comprises the peptide derivate of SEQ ID NO: 27.

Fang et al. teach a pharmaceutical composition comprising a DDK-8 peptide which encompasses the instantly claimed peptide derivative shown as SEQ ID NO: 27 (column 7, lines 23+). Specifically, the patent teaches that CCK peptide derivatives have high receptor activity which will effect a single organ or patient syndrome such as psychotic dysfunction (column 1, lines 25+).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made combine the references so as to generate a pharmaceutical composition comprising the polychelate as taught by Margerium et al. conjugated to the CCK-8 peptide as taught by Fang et al. One would have been motivated to do so because Fang et al. teach that the CCK-8 peptide derivates are highly specific for the cholecystokinin receptor and may be useful for the treatment of psychotic dysfunction. Thus, one of ordinary skill in the art would have a reasonable expectation that by producing a pharmaceutical composition comprising the polychelate as taught by Margerium et al. conjugated to the CCK-8 peptide as taught by Fang et al., one would achieve a pharmaceutical composition with high specificity to the cholecystokinin receptor.

Claims 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Margerium et al. (WO 95/24225 A1, 1995) in view of Fang et al. (US 5,631,230) in further view of Bakker et al. (Life Sciences 1991; 49: 1583-1591).

Margerium et al. in view of Fang et al. teach, as applied to claims 12, 28-29 and 31 above, a pharmaceutical composition comprising a polychelate molecules such as DOTA conjugated to a CCK-8 peptide derivative.

Margerium et al. in view of Fang et al. do not explicitly teach that the polychelate is DTPA.

Bakker et al. teach a radiopharmaceutical composition for imaging tumors comprising DTPA as the metal chelate.

Thus, it would have been prima facie obvious to one or ordinary skill in the art at the time the invention was made to combine the references so as to substitute DOTA as taught by Margerium et al. in view of Fang et al. with DTPA as taught by Bakker et al. One would have been motivated to do so because each of the metal chelates have been individually taught in the prior art to be effective as a radiopharmaceuticals. Thus, one of ordinary skill in the art would have a reasonable expectation that by substituting DOTA as taught by Margerium et al. in view of Fang et al. with DTPA as taught by Bakker et al, one would achieve a radiopharmaceutical composition.

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

BF

12/11/2006